

## **REMARKS**

Reconsideration of this application, as amended, is respectfully requested.

### **Related patents and patent applications**

The Applicants wish to draw the Examiner's attention to the applicants' related co-pending applications and issued patents (see Appendix A) directed to nanoparticles and methods of preparation and use thereof. Office actions have already issued on many of the listed cases.

### **Claim amendments**

Claims 237-265 and 433-441 were originally pending in this application. Claims 241, 242, 251, 252, 264, and 265 were cancelled and claims 237, 243, 253, 254, and 433 were amended without prejudice or disclaimer and to further clarify the invention or to change the dependency from cancelled claims. Support for the amendments can be found in the application as originally filed. See, for instance, the cancelled claims and the specification, i.e., page 78, lines 22-26. Accordingly, no new matter has been introduced into this application as a result of the above amendment. Claims 237-240, 243-250, 253-263, and 433-441 are now pending in this application.

### **Priority claim**

The Examiner has commented on the priority claim for this case, alleging that there is no support for the subject matter of claims 243-265 and 433-441 in U.S. Application nos. 09/344,667; 09/240,755; PCT/US97/12783; or 60/031,809, filed July 29, 1996. Applicants respectfully traverse. The earliest priority claim is directed to USSN 60/031,809 (the '809 application). The remaining applications claim priority to the '809 application. The '809 application describes gold nanoparticle-oligonucleotide conjugates that are remarkably stable (no particle growth) under high salt concentrations and elevated temperatures, conditions that are required for hybridization reactions. See, for instance, page 29, lines 16-23 of the '809 application. In contrast, gold nanoparticles are unstable under such conditions and would undergo particle growth. See, for instance, page 32, lines 13-21, of the '809 application. In addition, the '809 application also describes nanoparticles having one or more types of

oligonucleotides. See page 21, lines 17-22 and instant claim 433. Complex formation between the nanoparticle-oligonucleotide conjugates and target under hybridization conditions has been described. See, for instance, page 30, line 9 to page 23 of the ‘809 application. Selective discrimination of mismatches using the nanoparticle-oligonucleotide conjugates have been shown. See the ‘809 application at page 16, line 3-18; and page 31, line 24 to page 32, line 4. The remaining applications, which claim priority from the ‘809 application, also provide support for the claims. Accordingly, the priority claim is proper and supports the pending claims for this application.

### **Information Disclosure Statement**

The Examiner stated that the non-literature references listed in the Information disclosure statements filed on November 6, 2003 and January 31, 2002 have not been received by the Patent Office. These references, however, were physically deposited with the Patent Office as acknowledged by the PTO stamped post-card. These references are now lost at the Patent Office. As requested by the Examiner, a second set of references for the statements will be transmitted to the Examiner separately.

### **Statutory double patenting rejections**

Claims 433 and 437-441 stand rejected under 35 U.S.C. section 101 as claiming the same invention as claims 21-25 of U.S. Patent No. 6,582,921. Applicants respectfully traverse. A comparison of the claim language of instant claim 433, as amended, and claim 21 of the ‘921 patent are different. Thus, the claims vary in scope and are not identical to each other. Withdrawal of this 35 U.S.C. section 101 (same invention) rejection is in order and is respectfully requested.

Claims 237-265 stand provisionally rejected under 35 U.S.C. section 101 as claiming the same invention as claims 237-265 and 433-446 of co-pending USSN 09/974,007. Applicants respectfully traverse this rejection. The claims of the instant application and the ‘007 application are different in terms of scope and thus are not identical to each other. For instance, claim 237 of the ‘007 application recites “at least two types of oligonucleotides” while claim 237 of the instant

application does not. Withdrawal of this 35 U.S.C. section 101 (same invention) rejection is in order and is respectfully requested.

Claims 237-242 stand provisionally rejected under 35 U.S.C. section 101 as claiming the same invention as that of claims 237-242 of co-pending 09/976,577. The aforementioned claims of the instant application and the ‘577 application are different in terms of scope and thus are not identical to each other. For example, composition claim 237 of the ‘577 patent recites process steps while no such steps appear in claim 237 of the instant application. Withdrawal of this provisional 35 U.S.C. section 101 (same invention) rejection against claims 237-242 based on claims 237-242 of the co-pending ‘577 application is in order and is respectfully requested.

Claims 433 and 437-441 stand provisionally rejected under 35 U.S.C. section 101 as claiming the same invention as that of claims 454-456 of co-pending application no. 10/410,324. The aforementioned claims of the instant application and the ‘324 application are different in terms of scope and thus are not identical to each other. Withdrawal of this provisional 35 U.S.C. section 101 (same invention) rejection against claims 433 and 437-441 based on claims 454-456 of the co-pending ‘324 application is in order and is respectfully requested.

### **Obviousness-type double patenting rejections**

The Examiner rejected the claims of the pending application in view of Applicant’s pending patent applications and issued patents. The rejections against the issued patents are as follows: Claims 237, 241, and 242 stand rejected under the judicially created doctrine of double patenting over claim 1 of U.S. Patent no. 6,361,944; Claims 237, 241, and 242 stand rejected under the judicially created doctrine of double patenting over claims 1, 2, 11 and 12 of U.S. Patent No. 6,495,324; Claims 237, 241-243, 251-253 and 264-265 stand rejected under the judicially created doctrine of double patenting over claims 1-4 of U.S. 6,417,340; Claims 237, 241-243, 251-253, 264, and 265 stand rejected under the judicially created doctrine of double patenting over claims 1, 2, 8-10, 22-26, and 31-34 of U.S. Patent No. 6,506,564; Claims 433 and 437-441 stand rejected under the judicially created doctrine of double patenting over claims 1-10, 13, 16-19 of U.S. Patent No. 6,582,921; Claims 237, 241, and 242 stand rejected under the judicially created doctrine of double patenting over claims 1, 2, 5, and 6 of U.S. Patent No. 6,610,491; Claims 237, 241-243, 251-253, 264, 265, 433, and 440 are provisionally rejected

under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2, 8, 23, 24, 29, 42, and 113 of co-pending USSN 09/923,625 (now U.S. Patent No. 6,773,884); Claims 237-265 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 433-439, 449-453, 461-486, 496-500, and 508-521 of co-pending USSN 09/957,318 (now U.S. Patent no. 6,759,199); Claims 237, 241-243, 251-253, 264-265, 433, and 438-441 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 80-83, and 438-439 of co-pending USSN 09/966,312 (now U.S. Patent no. 6,673,548); Claims 237,241-243, 251-253, and 264-265 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 85-89, 150-154, and 433-436 of co-pending USSN 09/967,409 (now U.S. Patent no. 6,740,491); Claims 237, 241-243, 251-253, and 264-265 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 433, 443-445, 454-455, 464, 473, 474, 484, 493, 502, and 512 of co-pending USSN 09/974,500 (now U.S. Patent no. 6,709,825).

The rejections against the pending applications are as follows: Claims 237 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 155, 170 of co-pending USSN 09/975,384; Claims 237, 241-243, 251-253, and 264-265 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 433-436, 446-448, 458-461 of co-pending USSN 09/975,498; Claims 237, 243, and 253 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 433, 446, and 461-486 of co-pending USSN09/975,059 (now allowed); Claims 237-265 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 433, and 443-461 of co-pending USSN 09/976,601; Claims 237, 241, and 242 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 433, 435, 437, 445, 454-457, and 460-465 of co-pending USSN 10/410,324; Claims 237-265 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 433-462 of co-pending USSN 09/976,971 (now U.S. Patent no. 6,682,895); Claims

237-265 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 433-435, 489-500, 508-522, 531-536, and 546-556 of co-pending USSN 09/976,863; Claims 237-265, 433-441 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 8, 11, 433, 435, 436, and 442-444 of co-pending USSN 09/981,344 (now U.S. Patent no. 6,777,186); Claims 237-265 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 407, 409-410, 433, 435-436, 442-445, 450, 452-453, and 466-483 of co-pending USSN 09/976,900 (now allowed); Claims 237-265, and 433-441 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 243-265, and 433-446 of co-pending USSN 09/976,618 (now allowed).

The Applicants had already submitted a terminal disclaimer to obviate the rejection with respect to U.S. Patent no. 6,417,340. A copy of that terminal disclaimer is attached. The Applicant is submitting a second terminal disclaimer for the aforementioned U.S. Patents and a second terminal disclaimer to obviate the rejection with respect to pending applications. In view of the terminal disclaimers, the Applicants submit that withdrawal of the obviousness-type double patenting rejection is in order and is respectfully requested.

#### **Rejections under 35 U.S.C. section 102(b) and (e)**

The Examiner had rejected the claims for anticipation based on several references. As a general rule, for prior art to anticipate under section 102, every element of the claimed invention must be identically disclosed in a single reference. Corning Glass Works v. Sumitomo Electric, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989). The exclusion of a claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. Connell v. Sears, Roebuck & Co., 220 U.S.P.Q 193, 1098 (Fed. Cir. 1983). Applicants respectfully submit that none of the references cited against the pending claims can be applied to support an anticipation rejection of the claims under 35 U.S.C. sections 102 (b) and (e).

The Examiner rejected claims 237-241, 243-246, 248-251, 253-257, and 259-264 under 35 U.S.C. section 102(b) as being anticipated by Coffer et al. (Nanotechnology, Vol. 3, pp. 69-76)(1992) (“Coffer”). The Examiner alleged that the claims are anticipated because Coffer

allegedly teaches attachment of an oligonucleotide to a semiconductor particle at a surface density so that the nanoparticles are stable. The Applicants respectfully traverse.

While Coffer relates to the stabilization of cadmium quantum dots by attachment of DNA, Coffer does not define what is meant by the term stabilized other than “storage for 18 months at 4C”. As recited in claim 237, the term “stable under hybridization conditions” which are conditions that nanoparticles are not stable and would aggregate or undergo particle growth. Typical conditions of a hybridization experiment include elevated temperatures, salts, organics such as formamide and even exposure to reducing agents. See the specification at page 78, lines 22-28 and Examples. None of these conditions are taught by Coffer. Moreover, Coffer does not teach anything about spacer portions, recognition sequences or covalent attachment as recited in the claims.

Claims 237-240, 243-246, 248-250, 253-257, and 259-263 stand rejected under 35 U.S.C. section 102(b) as being anticipated by Chavany et al. (Pharmaceutical Research (1994), vol. 11(9), pp. 1370-1378 (“Chavany”). The Examiner alleged that Chavany teaches attachment of an oligonucleotide to a nanoparticle at a surface density sufficient such that the nanoparticles are stable. Specifically, the Examiner points to pages 1370-1372, 1375, and 1377 for support. The Applicants respectfully traverse this rejection.

Regarding the prior art rejection based on Chavany et al., Chavany states the following in his abstract:

Oligonucleotides can be adsorbed on polyisohexylcyanoacrylate nanoparticles in the presence of hydrophobic quarternary ammonium salts. Oligonucleotides bound to nanoparticles are protected from nuclease attack both in buffer and in cell culture media. ....Intracellular stability towards nucleolytic degradation is increased in the presence of nanoparticles. These results show that nanoparticles can be considered as convenient carriers for the protection and delivery of oligonucleotides to cells.

Thus, Chavany teaches that oligonucleotides are protected from enzymatic cleavage, once they have been attached to the polyisohexylcyanoacrylate nanoparticles. This disclosure has nothing to do with the claimed invention which is directed to nanoparticles that are stabilized as a consequence of oligonucleotide attachment at a sufficient surface density, not the other way

around. Moreover, Chavany does not teach or suggest anything about spacer portions, recognition sequences, or diluent oligonucleotides. Accordingly, withdrawal of the 35 U.S.C. section 102(e) rejection of claims 237-240, 243-246, 248-250, 253-257, and 259-263 based on Chavany is in order and is respectfully requested.

Claims 237-265 stand rejected under 35 U.S.C. section 102(e) as being anticipated by Kossovsky et al. U.S. Patent No. 5,460,831 (“Kossovsky”). The Examiner alleged that Kossovsky teaches attachment of oligonucleotide to gold nanoparticles at a surface density sufficient so that the nanoparticles are stable. Specifically, the Examiner points to the abstract, col. 3-4 and Examples 1-13. The Applicants respectfully traverse this rejection.

The rejection based on Kossovsky is inappropriate. Kossovsky teaches the attachment of DNA and RNA to biodegradable nanoparticles for the purpose of transfection. Kossovsky was concerned with protecting the nucleic acid in order to get it into the cell without degradation and loss of biological activity. See, for instance, col. 4, line 34, which states that: “...DNA and RNA segments may be attached to the core particles without significant loss of activity or denaturation.” Kossovsky does not teach or suggest that the nanoparticle transfection vectors are stable under hybridization conditions. Thus, there is nothing in Kossovsky that would teach or suggest nanoparticles that are stabilized by oligonucleotide attachment at a sufficient surface density as presently claimed. Moreover, Kossovsky does not teach or suggest anything about spacer portions, recognition sequences, or diluent oligonucleotides as presently claimed. Accordingly, withdrawal of the 35 U.S.C. section 102(e) rejection of claims 237-265 based on Kossovsky is in order and is respectfully requested.

Claims 237-265 stand rejected under 35 U.S.C. section 102(e) as being anticipated by Kausch et al. U.S. Patent No. 5,665,582 (“Kausch”). The Examiner alleged that Kausch teaches attachment of oligonucleotide to gold nanoparticles at a surface density sufficient so that the nanoparticles are stable. Specifically, the Examiner points to the abstract, col. 4-10, 17-19, 24 and Examples 1, 2, and 4-8 for support. The Applicants respectfully traverse this rejection.

The rejection based on Kausch also appears inappropriate. Kausch teaches various means of attaching biological materials – DNA and protein – to surfaces for the purpose of separation. Kausch does not provide any teachings or suggestion of any nanoparticles having oligonucleotides at a surface density such that nanoparticles are stable under hybridization

conditions. Since Kausch does not deal with gold nanoparticle-oligonucleotide conjugates but with solid surfaces, there can be no disclosure or suggestion of the stabilization of gold nanoparticle particles. Moreover, Kausch does not teach or suggest anything about spacer portions, recognition sequences, or diluent oligonucleotides as presently claimed. Accordingly, withdrawal of the 35 U.S.C. section 102(e) rejection of claims 237-265 based on Kausch is in order and is respectfully requested.

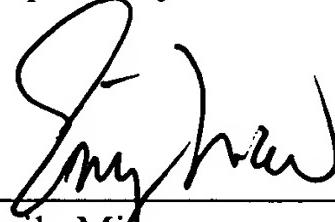
Claims 237-265 stand rejected under 35 U.S.C. section 102(e) as being anticipated by Yguerabide et al. U.S. Patent No. 6,214,560 ("Yguerabide"). The Examiner alleged that the claims are anticipated because Yguerabide allegedly teaches nanoparticles having low and high surface densities and nanoparticles having oligonucleotides attached thereto. The Applicants respectfully traverse this rejection.

It should be noted that the Examiner has alleged teachings of "**particle** surface density" in the '560 patent. The discussion is allegedly found starting in column 82, line 35, in Yguerabide. In column 83, lines 11-21, Yguerabide discusses that such particles can be metal-like particles. Column 83 provides further discussion regarding particle size and particle binding to a surface. There is no discussion of any surface density of oligonucleotides present on the surface of the particles anywhere in Yguerabide. Moreover, Yguerabide does not teach or suggest anything about spacer portions, recognition sequences, or diluent oligonucleotides as presently claimed. Accordingly, withdrawal of the 35 U.S.C. section 102(e) rejection of claims 237-265 based on Yguerabide is in order and is respectfully requested.

In conclusion, the Applicants respectfully submit that the claims in this application are in allowable condition and request a Notice to this effect.

Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited. The Examiner is invited to contact the undersigned representative if the Examiner believes that this would be helpful in expediting the prosecution of this application.

Respectfully submitted,



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**TERMINAL DISCLAIMER TO OBLVIAE A DOUBLE  
PATENTING REJECTION OVER A PRIOR PATENT**

Docket No. 00-713-i-12

In Re Application of: Mirkin et al.

Application No.: 09/975,376

Filed: Oct. 11, 2001

For: Nanoparticles having oligonucleotides attached thereto and uses therefor

**COPY**

The owner\*, Nanosphere, Inc., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173 as shortened by any terminal disclaimer, of prior Patent No. 6,417,340. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of any prior patent, as presently shortened by any terminal disclaimer, in the event that it later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

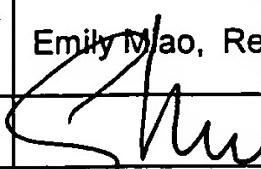
Check either box 1 or 2 below, if appropriate.

1.  For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2.  The undersigned is an attorney or agent of record.

- Terminal disclaimer fee (\$ 110 ) under 37 CFR 1.20(d) is included.

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Signature	
Date	November 6, 2003

\*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).